Reduced Use of Illicit Substances, Even Without Abstinence, Is Associated With Improved Depressive Symptoms Among People Living With HIV

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Purpose: Substance use is linked with poor outcomes among people living with HIV (PLWH) and is associated with mental health disorders. This analysis examines the impact of decreasing substance use, even without abstinence, on depressive symptoms among PLWH.

Methods: Data are from PLWH enrolled in the Centers for AIDS Research Network of Integrated Clinical Sites cohort. Participants completed longitudinal assessments of substance use (modified ASSIST) and depressive symptoms (PHQ-9). Changes in substance use frequency were categorized as abstinence, reduced use, and nondecreasing use. Adjusted linear mixed models with time-updated change in substance use frequency and depressive symptom scores were used to examine associations between changes in the use of individual substances and depressive symptoms. Analyses were repeated using joint longitudinal survival models to examine associations with a high (PHQ-9 ≥10) score.

Results: Among 9905 PLWH, 728 used cocaine/crack, 1016 used amphetamine-type substances (ATS), 290 used illicit opiates, and 3277 used marijuana at baseline. Changes in ATS use were associated with the greatest improvements in depressive symptoms: stopping ATS led to a mean decrease of PHQ-9 by 2.2 points (95% CI: 1.8 to 2.7) and a 61% lower odds of PHQ-9 score ≥10 (95% CI: 0.30 to 0.52), and decreasing ATS use led to a mean decrease of 1.7 points (95% CI: 1.2 to 2.3) and a 62% lower odds of PHQ-9 score ≥10 (95% CI: 0.25 to 0.56). Stopping and reducing marijuana and stopping cocaine/crack use were also associated with improvement in depressive symptoms.

Conclusions: We demonstrated that both substance use reduction and abstinence are associated with improvements in depressive symptoms over time.

Key Words: HIV, substance use, methamphetamines, depressive symptoms

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INTRODUCTION

Substance use is a public health challenge in the United States among many different vulnerable populations. Substance use is associated with a range of comorbidities among people living with HIV (PLWH), including viral hepatitis, tuberculosis, bacterial infections, kidney disease, atherosclerosis, cancer, and mental health disorders.[1]

In particular, current substance use is associated with increased rates of depressive symptoms and depression among PLWH.[2–7] Managing mental health disorders is

challenging and, if untreated, the mental health disease will negatively impact HIV care along the HIV care continuum, including delayed linkage to care, delayed initiation of antiretroviral therapy, suboptimal medication adherence, and worse clinical outcomes.[3] Achieving abstinence in PLWH with substance use disorders is challenging,[1] often requiring multifaceted and interdisciplinary approaches. Addressing substance use, however, is a key intervention for improving depressive symptoms in PLWH, especially because these conditions often co-occur and impact the HIV care continuum.[1–7]

We hypothesized that a reduction in substance use may have benefits in terms of depressive symptoms, even if abstinence is not achieved. Substance use can be considered a process of negative reinforcement, due to a decrease in the function of normal reward-related neurocircuitry, which results in increased depressive symptoms among users.[8] Previous studies, however, have predominantly focused on achieving complete abstinence, which is often the main goal of substance use treatment. Harm reduction, the reduction in drug use, remains an important goal, but it is crucial to determine whether such reductions have resultant improvements in health, including depression outcomes. Our objective was to evaluate the impact on depressive symptoms of reducing substance use, with or without achieving abstinence. We considered this question in PLWH enrolled in the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort.[9]

METHODS

This study includes PLWH aged 18 years or older and enrolled at 1 of 6 CNICS sites (Johns Hopkins University; University of Alabama at Birmingham; University of California, San Diego; University of California, San Francisco; University of North Carolina at Chapel Hill; and University of Washington, Seattle). CNICS is a longitudinal observational study of PLWH receiving primary care at CNICS sites from January 1, 1995, to the present.[9] In total, 9905 participants were eligible for inclusion in analyses.

All participants completed longitudinal assessments of substance use frequency including cocaine/crack; amphetamine-type substances (ATS) that included methamphetamines; illicit opioids; and marijuana. Participants had to have 2 or more substance use assessments during cohort follow-up to be eligible for this study. We formed subcohorts of participants who were using a specific substance to ensure measurement of reduced use or abstinence were performed among participants eligible to reduce use due to current use.

As a sensitivity analysis, to enrich the number of opioid users, we also pooled CNICS with Project STRIDE[10] from the Seek, Test, Treat, and Retain cohort.[10] Project STRIDE is a randomized controlled trial of PLWH with substance use disorders that includes a buprenorphine plus naloxone (BPN) intervention, is registered at www.clinicaltrials.gov (NCT 01550341), and has similar measures of depressive symptoms and substance use (making it ideal for pooling).

Substance Use

In the CNICS cohort, PLWH completed an approximately 10-minute clinical assessment with touchscreen tablets, with a planned frequency of every ~6 months, as part of routine clinical care.[11] The CNICS clinical assessment includes measures of substance use (modified Alcohol, Smoking, and Substance Involvement Screening Test)[12] as well as a broad group of other patient-reported measures and outcomes (including alcohol use). Assessments of substance use included a Likert scale for frequency of use in the past 30 days.

We categorized frequency of use into less than weekly, 1–3 times per week, and daily or almost daily, based on participant responses to the study instruments. Changes in substance use frequency were defined as a change from one category to another. Possible changes included abstinence (change to no use), reduced use (change to a lower frequency category), and nondecreasing or increasing use (the same or higher category of use, as compared to baseline).

Depressive Symptoms

Depressive symptom scores were assessed using the Patient Health Questionnaire (PHQ)-9. CNICS administered the PHQ-9 to participants repeatedly over follow-up, through a Computer-Assisted Self-Interview (CASI) system. The PHQ-9 has been validated as a scale for detecting depressive symptoms both in outpatient populations[13] and in diverse/international populations.[14] It has high screening utility and is used in clinical care to screen for depression among PLWH.[15,16]

Statistical Models

Linear mixed models with time-updated change in substance use frequency and depressive symptom scores were used to examine associations between changes in the use of individual substances and depressive symptoms. For each substance, a specific cohort was formed of participants who were users at study baseline. These models were adjusted for other substance use, with random slopes and intercepts at the participant level to handle repeated measures over follow-up of both substance use and depressive symptoms. This type of mixed-model approach to link changes in drug exposure levels to changes in continuous outcomes has been used in pharmacoepidemiology contexts[17] and is a well-known approach to handle irregular data collection and participants lost to follow-up.[18,19] All estimates were adjusted for age, sex, use of other substances, alcohol use, and calendar year.

We were also interested in whether findings were the same if the outcome of interest was screening positive for depression rather than change in depression symptom score as a continuous variable. Therefore, we dichotomized depression scores using a cutoff point of ≥10 (high PHQ-9) to indicate high predictive value for screening positive for depression[20] and repeated analyses using a joint longitudinal and survival model[21] to examine the impact of decreasing drug use and of abstinence for each drug due to known limitations with less complex models.[22]

We also considered the possibility of a bidirectional association. We examined change in days of substance use among participants experiencing a drop in PHQ-9 score over follow-up, using a linear mixed-model approach. All statistical analysis was performed in STATA 14 (StataCorp, 2017, Stata Statistical Software: Release 15, College Station, TX: StataCorp LLC).

RESULTS

CNICS enrolled patients in clinical care, resulting in a large diverse cohort. Among 9905 PLWH, the mean age was 44 years, 16% of participants were female, and 40% used a substance at baseline (Table 1). Overall, 728 participants reported cocaine/crack use, 1016 ATS use, 290 illicit opioid use, and 3277 reported marijuana use at baseline.

Changes in ATS use were associated with the greatest improvements in depressive symptoms. Abstinence from ATS was associated with a mean difference in the depressive symptom score of Δ −2.2 PHQ-9 points [95% confidence interval (CI): −2.7 to −1.8] or a 61% lower odds of screening positive for depression (95% CI: 0.30 to 0.52) compared with those who continued their ATS use without a decrease in frequency. Decreasing ATS without abstinence was associated with a mean difference of Δ −1.7 PHQ-9 points (95% CI: −2.3 to −1.2) or 62% lower odds of screening positive for depression (95% CI: 0.25 to 0.56) compared with those who did not decrease their use (Table 2).

Decrease in use of other substances had more modest associations with depressive symptoms. Stopping marijuana was associated with a mean decrease in the depressive symptom score of Δ −0.5 PHQ-9 points (95% CI: −0.7 to −0.3) or 28% lower odds of screening positive for depression (95% CI: 0.58 to 0.88), and decreasing marijuana use was associated with a mean decrease of Δ −0.4 PHQ-9 points (95% CI: −0.7 to −0.1) or 30% lower odds of screening positive for depression (95% CI: 0.59 to 0.84). Stopping cocaine/crack was associated with a mean difference in the PHQ-9 score of Δ −0.8 points (95% CI: −1.3 to −0.4) or 24% lower odds of screening positive for depression (95% CI: 0.56 to 1.03); however, decreasing cocaine/crack use without abstinence was not associated with a significant change in PHQ-9 score or the odds of screening positive for depression [ΔPHQ-9 score = −0.5 points/odds ratio (OR) = 0.97]. Finally, neither stopping or reducing use of opiates over follow-up was associated with a significant reduction of depressive symptom (ΔPHQ-9 score = −0.6 points/OR = 0.79 and ΔPHQ-9 score = −0.5/OR = 1.20, respectively) (Table 2). Results for opioid use were similar to the CNICS-only results (Table 2) when we included an additional study, Project STRIDE, with a high-level of opioid use to improve precision on the illicit opioid estimates (Table 1, Supplemental Digital Content, http://links.lww.com/QAI/B196).

Looking for a bidirectional association, we considered the association between reducing PHQ-9 score over follow-up and frequency of substance use. There was an association for cocaine/crack (Δdays of cocaine/crack use −0.07; 95% CI: −0.12 to −0.02), ATS (Δdays of ATS use −0.21; 95% CI: −0.30 to −0.13), and marijuana (Δdays of marijuana use −0.25; 95% CI: −0.44 to −0.06) but not for opiates (Δdays of opiate use −0.03; 95% CI: −0.08 to 0.02) (Table 2, Supplemental Digital Content, http://links.lww.com/QAI/B196, individual logistic and survival models, by substance, are Tables 3–10, Supplemental Digital Content, http://links.lww.com/QAI/B196).

TABLE 1. Demographic and Clinical Characteristics for 9905 People Living With HIV From the CNICS Cohort, Including Days of Use Scaled to a 30-Day Period

	CNICS
Age at baseline, mean (SD)	44 (11)
Female	16%
Race/ethnicity	
White	48%
Black	33%
Hispanic	14%
Other/missing	5%
Current use of cocaine/crack	7%
Mean days of cocaine/crack use (among users)	3 (7)
Current use of ATS	10%
Mean days of ATS (among users)	6 (11)
Current illicit opiate use	3%
Mean days of illicit opiate use (among users)	6 (11)
Current marijuana use	33%
Mean days of marijuana use (among users)	12 (14)
Current alcohol use	67%
Mean days of alcohol use (among users)	5 (6)
Current binge alcohol use	34%
Mean days of binge alcohol use (among users)	2 (6)
Depression (PHQ-9 score)	6 (6)

DISCUSSION

We demonstrated that both substance use reduction and abstinence are associated with improvements in depressive symptoms over longitudinal follow-up in PLWH. Relative to other substances, reducing ATS use was more strongly associated with alleviation of depressive symptoms, perhaps suggesting that it has greater detrimental clinical impact, including on depression, than other drugs in this population.

Our results showing that cessation of substance use is associated with improved depression scores are not surprising, although it was reassuring to see the level of concrete improvement in routine care environments. It is well known that depression is associated with substance use.[23–25] There is also evidence that substance use may interfere with pharmacologic treatment for depression in PLWH, resulting in less benefit of depression treatment in randomized trials,[26] although there may be less impact for cognitive–behavioral therapy.[27,28]

Treatment for depression in PLWH is important because depression is a known barrier to HIV medication adherence[29,30] and a source of morbidity and mortality in its own right.[31,32] Substance use interferes with improving depression and should be addressed as a part of any treatment plan. Our results should provide additional support for studying interventions that lead to

TABLE 2. The Association of Substance Use Change With Depressive Symptoms as Measured With the PHQ-9 (Screen Positive PHQ-9 Score or Linear PHQ-9 Score) Among Persons Living With HIV in Clinical Care Across the United States in the CNICS Cohort Between 2010 and 2017

	Joint Longitudinal and Survival Model (PHQ-9 Score ≥10 Outcome)			Linear Mixed Models (Linear PHQ-9 Score Outcome)		
	OR	95% CI	*P*	ΔPHQ-9 Score	95% CI	*P*
Cocaine/crack						
Decrease	0.97	0.60 to 1.58	0.912	−0.53	−1.36 to 0.31	0.215
Quit	0.76	0.56 to 1.03	0.080	−0.80	−1.26 to −0.35	0.001
ATS						
Decrease	0.38	0.25 to 0.56	<0.001	−1.73	−2.27 to −1.20	<0.001
Quit	0.39	0.30 to 0.52	<0.001	−2.23	−2.65 to −1.81	<0.001
Opioids						
Decrease	1.20	0.39 to 3.72	0.746	−0.17	−1.82 to 1.47	0.838
Quit	0.79	0.48 to 1.29	0.352	−0.60	−1.35 to 0.14	0.112
Marijuana						
Decrease	0.72	0.58 to 0.88	0.002	−0.40	−0.66 to −0.13	0.003
Quit	0.70	0.59 to 0.84	<0.001	−0.50	−0.72 to −0.27	<0.001

All estimates are adjusted for baseline frequency of use of other substances (ATS, cocaine/crack, opiates, and marijuana), alcohol use, binge alcohol use, age, sex, and time (years) since baseline. The number of baseline users in each subcohort varied based on the number of active substance users: cocaine/crack N = 728, ATS N = 1,016, opiates N = 290, marijuana N = 3277.

reductions in substance use among PLWH even when complete abstinence is not feasible.

Bidirectional associations seem to be present, in that participants who reduced their PHQ-9 score over follow-up also had fewer days of substance use for most substances. Although in clinical care there is often an emphasis on substance use cessation before diagnosis and treatment of mental health disorders due to the confounding impact of substance use on diagnosis of mental health disorders, treatment for depression can be effective in people with substance use disorders,[33] including PLWH.[26] These results suggest that there may also be a role for treating depression in parallel with efforts to treat substance use disorders.

Our study had key strengths including the longitudinal nature of the data and the high-quality measures of both our exposure and outcome. The use of linear mixed models allowed us to account for the irregular nature of the data and loss to follow-up in this population.

Our study had several key limitations. The population in these studies had lower levels of opioid use than other substances; so, we may have been underpowered to detect opioid associations. The study is inherently observational and although we adjusted our estimates for obvious confounders, the possibility of residual confounding remains. The measures of substance use were self-reported and were collected using categories of frequency of use, preventing us from establishing a clear threshold for reduction in order for participants to show benefit.

The results of this study suggest that reduction in substance use can result in better psychological outcomes for PLWH dealing with depressive symptoms. These benefits are particularly striking among ATS users (mostly methamphetamine), who showed the greatest benefits from cessation or reduction of use. Although clearly cessation of substance use should remain the target of public health interventions, our findings show that reduction in level of use also confers benefit for PLWH dealing with substance use issues.

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